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Asymmetric Synthesis with Sugar Derivatives. III.[1] Action of Methylmagnesium Iodide on Sugar Esters of Phenylglyoxylic Acid

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Asymmetric synthesis of atrolactic acid was investigated by the reaction of methylmagnesium iodide with phenylglyoxylic ester containing such an optically active component as 1, 2 ; 5, 6-di-*O*-cyclohexylidene-D-glucose, its isopropylidene derivative 5-*O*-ethyl-1, 2-*O*-isopropylidene-D-xylose, its 5-deoxy-5-*S*-ethyl derivative, or 5-deoxy-1, 2-*O*-isopropylidene-D-xylose. All of the resulting sugar atrolactates were very easily hydrolyzed with alkali at room temperature to afford the levorotatory acid in 22—38% optical yield. The asymmetric reactions proceeded in accordance with Prelog's rule, but a Prelog's scheme for asymmetric induction was slightly modified when the steric course for 3-*O*-phenylglyoxyloyl-1, 2 ; 5, 6-di-*O*-cyclohexylidene- and -isopropylidene-D-glucose was discussed.

Previous publications[1,2] have described the asymmetric syntheses by the reactions of some sugar esters with organometallic compounds. The remarkable effects of the sugar derivatives on the optical yields or steric course of the asymmetric conjugate addition of Grignard reagent were observed, while the role of sugar derivatives as optically active alcohols in asymmetric syntheses has not been fully elucidated. It seemed, therefore, desirable to investigate an asymmetric synthesis of atrolactic acid (2-hydroxy-2-phenylpropionic acid) *via* the reactions of phenylglyoxylic esters of sugar derivatives with methylmagnesium iodide. Phenylglyoxylic esters containing numerous types[3] of optically active alcohols as an ester-component have been employed in the asymmetric synthesis of atrolactic acid, wherein Prelog's rule[3a] has been well established.

In the present experiments 1, 2 ; 5, 6-di-*O*-cyclohexylidene-D-glucose[4] and its isopropylidene derivative,[5] 5-*O*-ethyl-1, 2-*O*-isopropylidene-D-xylose and its 5-deoxy-5-*S*-ethyl derivative,[6] and 5-deoxy-1, 2-*O*-isopropylidene-D-xylose[7] were used as optically active alcohols, which were readily prepared by the standard methods. The corresponding 3-*O*-phenylglyoxyloyl derivatives (Ia—Ie) were synthesized by the reactions of the sugars with phenylglyoxyloyl chloride in pyridine. These yields, physical properties, and analyses are summarized in Table 2.

Procedure

The procedure (Methods A and B) of asymmetric synthesis of atrolactic acid (III) was slightly modified from the method of Prelog.[3b] Thus, an ethereal solution of the sugar ester was added during 5 min to a same solution of methylmagnesium iodide (3 mol eq.) at −5—0°C with stirring. After the stirring was continued for another 5 min, the diastereomeric mixture (II-R and II-S) was treated with aqueous ammonium chloride, and the resulting atrolactate was hydrolyzed with potassium hydroxide to liberate optically active acid (III) (Method A).

Although the keto carbonyl group reacts with Grignard reagent faster than the ester carbonyl group in general, II-R and II-S might suffer from the attack of the excess reagent to form products other than II under the above reaction conditions. If this undesirable side reaction proceeded, the ratio of II-R to II-S resulting from only the normal addition might be altered and consequently there might be some uncertainty[3c,3i] as to the direction or the optical yield of the asymmetric synthesis.

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[1] Part II. M. Kawana and S. Emoto, This Bulletin, **40**, 618 (1967).

[2] M. Kawana and S. Emoto, *ibid.*, **39**, 910 (1966).

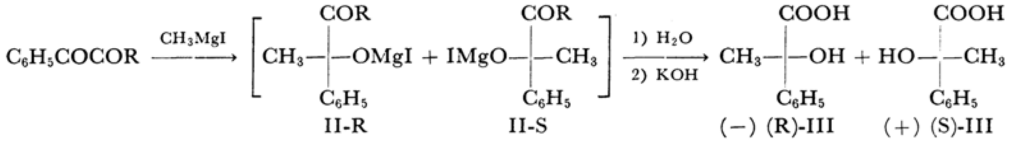
[3] a) V. Prelog, *Helv. Chim. Acta*, **36**, 308 (1953), and references cited therein. b) V. Prelog and H. L. Meier, *ibid.*, **36**, 320 (1953). c) W. G. Dauben, D. F. Dickel, O. Jeger and V. Prelog, *ibid.*, **36**, 325 (1953). d) V. Prelog and G. Tsatsas, *ibid.*, **36**, 1178 (1953). e) V. Prelog, O. Ceder and M. Wilhelm, *ibid.*, **38**, 303 (1955). f) V. Prelog, Eva Philibin, E. Watanabe and M. Wilhelm *ibid.*, **39**, 1086 (1956). g) K. Mislow, V. Prelog and H. Scherrer, *ibid.*, **41**, 1410 (1958). h) W. R. Feldman and V. Prelog, *ibid.*, **41**, 2396 (1958). i) J. A. Berson and M. A. Greenbaum, *J. Am. Chem. Soc.*, **80**, 445 (1958). j) W. Acklin and V. Prelog, *Helv. Chim. Acta*, **42**, 1239 (1959).

[4] R. C. Hockett, R. E. Miller and A. Sacttergood, *J. Am. Chem. Soc.*, **71**, 3072 (1949).

[5] W. L. Glen, G. S. Myers and G. A. Grant, *J. Chem. Soc.*, **1951**, 2568.

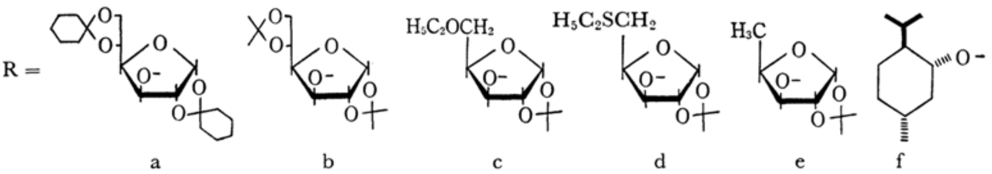
[6] A. L. Raymond, *J. Biol. Chem.*, **107**, 85 (1934).

[7] P. A. Levene and J. Compton, *ibid.*, **111**, 325 (1935).



$$C_6H_5COCOR \xrightarrow{CH_3MgI} \left[CH_3-\overset{COR}{\underset{C_6H_5}{|}}-OMgI + IMgO-\overset{COR}{\underset{C_6H_5}{|}}-CH_3 \right] \xrightarrow[2)\ KOH]{1)\ H_2O} CH_3-\overset{COOH}{\underset{C_6H_5}{|}}-OH + HO-\overset{COOH}{\underset{C_6H_5}{|}}-CH_3$$

II-R II-S (−) (R)-III (+) (S)-III



Therefore, method B was carried out, in which the ethereal solution of the sugar ester was added during longer period (40 min) with stirring for additional 1 hr. If the normal addition products, II-R and II-S, were considerably consumed at unequal rates by the side reaction, the optical or synthetic yield of III or its sign of rotation would have to be different between the results of methods A and B.

"Inverse addition" of the Grignard reagent to an ethereal solution of the sugar ester was unsuccessful because of the formation of ether-insoluble materials. The reaction of (−)-menthyl phenylglyoxylate (If) was also repeated under our conditions.

Results and Discussion

The results of asymmetric synthesis of III are shown in Table 1. The optical⁸⁾ and synthetic yields by method A were slightly higher than those by method B except the optical yields in the case of Id; the side reaction of the Grignard addition occurred to an appreciable extent under the experimental conditions. However, differences of the optical yields between the methods A and B were identical within experimental error. It, therefore, seemed likely that the side reaction could be neglected on considering the steric course of the Griganrd addition to the keto carbonyl group. In each case, (−)-acid (III) having R-configuration⁹⁾ was predominantly produced, and 1, 2 ; 5, 6-di-*O*-cyclohexylidene derivative (Ia) was the most effective for the optical yield (38.2%). The comparable optical yield of III with the same sign of rotation was observed in the use of (−)-menthyl ester (If).

TABLE 1. ASYMMETRIC SYNTHESIS OF 2-HYDROXY-2-PHENYLPROPIONIC ACID (III)

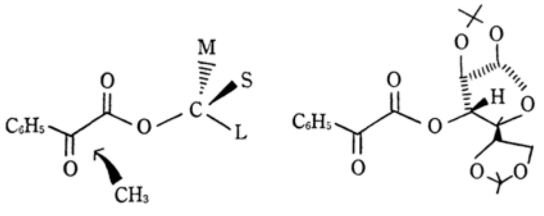
Ester	Method	Synthetic yield %	$[\alpha]^{20}_D$ (*c* in EtOH)	Optical yield*2 %
Ia	A	72.2	−14.4°(0.95)	38.2
	B	67.8	−14.1°(0.96)	37.4
Ib	A	78.6	−12.9°(0.95)	34.2
	B	77.4	−12.3°(0.93)	32.6
Ic*1	A	77.4	−10.6°(0.82)	28.1
	B	69.6	−10.4°(0.77)	27.6
Id	A	80.7	−9.5°(0.88)	25.2
	B	72.9	−9.8°(0.91)	26.0
Ie	A	77.1	−8.3°(0.83)	22.0
	B	75.3	−8.2°(0.92)	21.8
If	A	78.3	−11.5°(0.86)	30.5
	B	76.9	−11.0°(0.86)	29.2
	Prelog*3	92	−9.5°(7.17)	25

*1 When Ic was added to Grignard solution, white precipitates were appeared, which remained after the reaction had been completed.

*2 Calcd. based on $[\alpha]_D$ −37.7° for optically pure acid (III). Ref. 8.

*3 Ref. 3b.

The stereochemical course in the case of If is well known to be governed by Prelog's rule³ᵃ⁾; the methyl group enters into the keto carbonyl group from the least-hindered side of a transoidal coplanar configuration as shown in IV. The order of bulkiness of groups around the hydroxyl-bearing carbon atom in (−)-menthol is as follows: the largest group (L) is the methine substituted with isopropyl group, the medium-sized group (M) is the methylene, and the smallest group (S) is the hydrogen.



IV V

Stuart molecular model shows that the arrangement of L, M, and S-groups of the sugar derivatives employed corresponds to that of (−)-menthol: for example, Ib is depicted as V. From the experimental results, it seemed likely that the reactions of Ia—Ie with methylmagnesium

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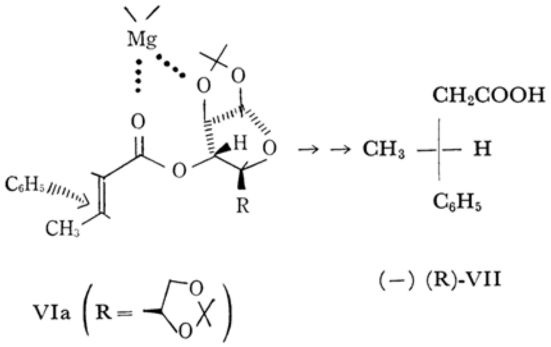
8) A. McKenzie and G. W. Clough, *J. Chem. Soc.*, **97**, 1016 (1910), reported $[\alpha]^{13.8}_D$ −37.7° (*c* 3.35, ethanol) for optically pure acid (III).

9) K. Freudenberg, J. Todd and R. Seidler, *Ann.*, **501**, 199 (1933); J. H. Brewster, *J. Am. Chem. Soc.*, **78**, 4061 (1956).

iodide proceeded in accordance with Prelog's rule.

However, if the conformation of V was the most favorable one at the present Grignard addition, the L-group would be possible to cover the S-group side (the S-side), because the 2, 2-dimethyl-1, 3-dioxolane ring in the L-group and the phenylglyoxyloxyloyl group are on the same side of the furanose ring. Consequently V should lead to a predominance of (+)-III rather than to the observed predominance of (−)-III. The similar stereochemical outcome[2] was previously obtained when 3-*O*-crotonoyl-1, 2; 5, 6-di-*O*-cyclohexylidene- or -isopropylidene-D-glucose (VIa) was treated with phenylmagnesium bromide. Contrary to Prelog's rule, the phenyl group entered predominantly into β-position of the double bond of VIa from the M-side to afford, after saponification, (−)(R)-3-phenylbutyric acid (VII) in 32% optical yield: (+)(S)-VII was produced in 5% optical yield when (−)-menthyl crotonate was used.[10]



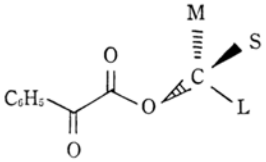
(−) (R)-VII

VIa

b ($R=CH_3$)

To explain this stereochemically inconsistent results between the sugar derivative and (−)-menthol, it has been presumed that the oxygen attached to C-2 of glucose co-ordinates[11] with the magnesium of Grignard reagent, which has partially bonded to the oxygen of the ester carbonyl group and diminished the electron density on the β-position of the carbon-carbon double bond in the crotonate. The large 2, 2-dimethyl-1, 3-dioxolane ring attached to C-4 of glucofuranose would be presumably compelled by such co-ordination to approach to the carbon-carbon double bond; in the case of the 3-*O*-crotonoyl-5-deoxy-1, 2-*O*-isopropylidene-D-xylose (VIb)[12] containing sterically smaller methyl group than the dioxolane ring of VIa, (+)-VII was obtained, after saponification, in 16% optical yield by the attack of phenyl group from the S-side.

The mechanism of Grignard addition to the keto carbonyl group does not involve the co-ordination of the reagent with the oxygen of ester carbonyl group. When the co-ordinations of the reagent with both oxygen atoms of the ester carbonyl and the sugar did not exist, the acid portion and 2, 2-dimethyl-1, 3-dioxolane ring attached to C-4 of glucofuranose would keep far away from each other because of steric hindrance between their substituents. Accordingly, modified Prelog's scheme as depicted in VIII is considered to be appropriate in discussing stereochemical course of the present asymmetric synthesis with 1, 2 ; 5, 6-di-*O*-cyclohexylidene or -isopropylidene-D-glucose. This scheme can apply to the case of the methoxymercuration of the sugar esters reported previously.[1] When the L-group in the sugar becomes smaller, the preffered conformation of the sugar ester will be similar to the normal Prelog's scheme (IV) and the relative bulkiness among the L, M, and S-groups will decrease to bring unsatisfactory results in optical yield.



VIII

Actually, the optical yield of III from Ie was the lowest one. It is interesting that the optical yield of III from Id involving ethylthio group was slightly lower than that from Ic containing ethoxyl group, but its reason is not clear.

Experimental

Optical rotations were measured with a Perkin-Elmer Model 141 photoelectric polarimeter (direct reading to ±0.002°) in a 1 dm tube. Infrared spectra were obtained using either a Perkin-Elmer Model 521 grating infrared spectrophotometer or a Shimadzu IRS-27 Model D. All melting and boiling points are uncorrected. Ascending thin layer chromatography was performed with ether - petroleum ether (30—70°C) (3 : 7, v/v) solvent system on a 250 μ layer of silica gel G (E. Merck, Darmstadt, Germany) activated for 2 hr at 120°C and the plates were sprayed with a mixture of methanol, sulfuric acid, and *p*-methoxybenzaldehyde (8.5 : 1 : 0.5, v/v) and were then heated.

(−)-Menthyl phenylglyoxylate (If) was prepared by the method of McKenzie,[13] mp 71.0—72.0°C, $[\alpha]_D^{20}$ −44.7° (*c* 1.04, ethanol) (lit.[13] mp 73—74°C, $[\alpha]_D^{20}$ −44.4° (*c* 4.78, ethanol)).

5-*O*-Ethyl-1, 2-*O*-isopropylidene - D - xylose. The procedure was modified from the method of Levene.[14]

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[10] Y. Inouye and H. M. Walborsky, *J. Org. Chem.*, **27**, 2706 (1962).

[11] Similar phenomena in asymmetric inductions have been reported; M. L. Wolfrom and S. Hanessian, *J. Org. Chem.*, **27**, 1800 (1962); D. J. Cram and D. R. Wilson, *J. Am. Chem. Soc.*, **85**, 1245 (1963); J. Yoshimura, Y. Ohgo and T. Sato, *ibid.*, **86**, 3858 (1964).

[12] It is presumed that the most stable ground state conformation of this compound is VIb; *cf.* Ref. 1.

[13] A. McKenzie, *J. Chem. Soc.*, **85**, 1249 (1904).

[14] P. A. Levene and A. L. Raymond, *J. Biol. Chem.*, **102**, 338 (1933).

TABLE 2. PHENYLGLYOXYLIC ESTERS OF SUGAR DERIVATIVES

Ester	Appearance	Yield %	$[\alpha]_D^{20}$ (c in benzene)	IR $\nu_{max}^{cm^{-1}}$ (in CCl_4) C_6H_5CO	OCOR	R_f*1	Molecular formula	C, % Found	C, % Calcd	H, % Found	H, % Calcd
Ia	glass	32	−32.4°(0.72)	1693	1750	0.68	$C_{26}H_{32}O_8$	66.15	66.08	6.67	6.83
Ib	glass	41	−46.0°(0.82)	1693	1750	0.48	$C_{20}H_{24}O_8$	61.11	61.21	5.97	6.17
Ic	oil	41	+0.3°(0.60)	1693	1745	0.42	$C_{18}H_{22}O_7$	61.72	61.70	6.19	6.33
Id	oil	50	−51.3°(0.67)	1693	1745	0.53	$C_{18}H_{22}O_6S$*2	58.94	59.00	6.12	6.05
Ie	oil	36	+56.4°(0.55)	1693	1741	0.51	$C_{16}H_{18}O_6$	62.83	62.74	5.74	5.92

*1 Standard: (−)-Menthol, R_f 0.44.

*2 S, %: Found 8.77; Calcd 8.75.

A suspension of 1, 2-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-D-xylose (13.8 g, 0.04 mol) in absolute ethanol (40 m*l*) was added to a sodium ethoxide solution which had been prepared from sodium (2.8 g, 0.12 mol) and absolute ethanol (100 m*l*).

The mixture was heated in an autoclave at 100°C for 4 hr. After the reaction mixture was allowed to stand overnight at room temperature, water (50 m*l*) was added and ethanol was evaporated. The precipitates were dissolved by adding water and the solution was extracted several times with chloroform. The combined chloroform extracts were washed with a small amount of water and dried. After removal of the solvent, the residue was distilled to yield 5.2 g (58.4%) of 5-*O*-ethyl-1, 2-*O*-isopropylidene-D-xylose, bp 120—121°C/2 mmHg, which solidified on cooling, mp 59.0—60.5°C; $[\alpha]_D^{25}$ −8.2° (c 0.51, benzene).

Found: C, 55.18; H, 8.24%. Calcd for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31%.

General Procedure of Esterifications of the Sugar Derivatives. Yields and physical properties of the esters obtained here are listed in Table 2.

To a solution of the sugar derivative (0.06 mol) in a mixture of dry pyridine (30 m*l*) and dry benzene (30 m*l*) was added a solution of phenylglyoxyloyl chloride (0.06 mol) in dry benzene (15 m*l*) at −5—0°C during 20 min with rapidly stirring, which was thereafter continued for 15 min and for additional 15 min at room temperature. After standing overnight at room temperature, the reaction mixture was poured onto ice water and extracted with ether. The ethereal extract was washed at first with water and then mixed with ice and washed successively with iced 3% aqueous sulfuric acid, cold water, dilute aqueous sodium bicarbonate and water, and dried. Evaporation of the organic solvents afforded a crude ester, which was thereafter chromatographed on a silica gel[15a] column with ether-petroleum ether (30—70°C) (3 : 7, v/v) to give a slightly impure ester. This product was used satisfactorily in the Grignard reaction.

An analytically pure product was obtained by the following chromatographic treatment. A solution of the crude ester (600 mg) in a mixture (3 m*l*) of ether-petroleum ether (30—70°C) (3 : 7, v/v) was chromatographed on a silica gel[15b] (45 g) column (25×180 mm). Elution with the same solvent gave a pure ester after drying in a rotary evaporator at 100°C under reduced pressure (3 mmHg) for 1 hr.

General Procedure of Asymmetric Synthesis of 2-Phenyl-2-hydroxypropionic Acid. The procedure was modified from the method of Prelog.[3b]

Mehthod A. A solution of the sugar ester (2.0 mmol) in absolute ether (5 m*l*) was added, during 5 min, to a solution of methylmagnesium iodide (6.0 mmol) in absolute ether (5 m*l*) at −5—0°C, with stirring, which was thereafter continued for 5 min. The reaction was run under an atmosphere of nitrogen. The reaction mixture was treated with iced and saturated aqueous ammonium chloride (25 m*l*) and extracted with ether (80 m*l*). The ethereal extract was washed with water and dried over anhydrous sodium sulfate. Evaporation of ether gave noncrystalline material whose infrared spectrum showed absence of the starting ester.

To a cooled solution of the product in methanol (5 m*l*), was added a solution of potassium hydroxide (300 mg, 5.3 mmol) in water (1 m*l*), and the mixture was allowed to stand with occasionally shaking for 1 hr at room temperature. After most of methanol had been evaporated under reduced pressure at room temperature, the resulting residue was diluted with water (15 m*l*), and the mixture was extracted with chloroform (70—200 m*l*) until the sugar in chloroform could not be detected by thin layer chromatography. The infrared spectrum of the extract did not show the presence of atrolactate. The crude sugar derivative was recovered from the extract in more than 90% yield.

The water layer was acidified with 6N hydrochloric acid (2 m*l*) and extracted with ether (50 m*l*). The ethereal extract was washed with a small amount of water and dried over anhydrous sodium sulfate. After evaporation of ether, the residue was dissolved in hot water (50 m*l*), and the solution was treated with charcoal (50 mg). Water was distilled at 65°C in a rotary evaporator under reduced pressure, and the residue was dissolved in ethanol (10 m*l*). After filtration of the solution and evaporation of ethanol under reduced pressure at 70°C, the acid (III) was obtained as crystals, whose infrared spectrum was identical with that of authentic sample.[3b,16]

Method B. The method used here was identical with that described for the method A except that when an ethereal solution of the sugar ester was added to an ethereal solution of methylmagnesium iodide, the addition was carried out during 40 min and the stirring was continued for another 1 hr.

The authors are indebted to Dr. H. Homma and his staffs for elemental analyses, Mr. T. Kurihara for measurements of infrared spectra, and Miss K. Noda for her helpful assistance.

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15) a) Wakogel C-200 b) Wakogel Q-22, Wako Pure Chem. Ind., Japan.

16) M. V. Grignard, *Compt. rend.,* **135**, 627 (1902).